

### New approaches and targets in psychiatry neuroplastic changes precede chronic antidepressant responses of the 5-HT<sub>4</sub> receptor agonist RS67333

It has been recently suggested that activation of 5-HT<sub>4</sub> receptors might possess antidepressant properties in rats after a 3 days treatment, indicating a new strategy for developing faster-acting antidepressants. In this regard, here we have evaluated in rat brain the expression of proteins related to neuroplasticity after a subacute RS67333 treatment and their correlate on behavioural paradigms. A 3-days treatment with RS67333 (1.5 mg/kg/day), previously shown to increase neurogenesis in dentate gyrus, induced an upregulation in the expression of BDNF (% increase = 64%;  $p < 0.05$ ) and pCREB/CREB ratio (% increase = 93%;  $p < 0.01$ ) in the hippocampus. A significant reduction in the forced swimming test (immobility time) was also observed after 3 (% red= 27%;  $p < 0.001$ ) and 7 (% red=29%;  $P < 0.001$ ) days of treatment. However, in the novelty-feeding suppressed test, a validated paradigm to predict chronic antidepressant efficacy, a significant reduction in the latency to feed (% red= 49%;  $p < 0.03$ ) was observed only after 7 days of treatment. Short-term treatment with RS67333 also failed to downregulate 5-HT<sub>4</sub> receptor-coupled adenylate cyclase activity. Our data suggest that neural proliferation-related changes induced by antidepressants precede clinical improvement. Furthermore, when compared to data regarding classical antidepressants, our results show that the activation of 5-HT<sub>4</sub> receptors could represent a good strategy for developing antidepressants with a minor onset of action.